Phenylbutazone: An Evaluation of Its Use

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• Phenylbutazone (Butazolidin®), one of the newer antirheumatic drugs, while providing varying degrees of symptomatic relief in various types of rheumatism, may also cause serious toxic side effects. It is most effective in acute gout, and slightly less so in rheumatoid arthritis, of both the spondylitic and peripheral types. Its use in degenerative arthritis is not indicated. Its toxic side effects include gastrointestinal upsets, edema, rash, stomatitis, purpura, hematuria, agranulocytosis and reactivation of peptic ulcer. Several fatalities have been reported. It is, however, a valuable drug if used properly. Extreme caution should be exercised in selection of patients, in administration of the drug and in continuous observation of patients receiving it.

A GREAT DEAL of controversy has arisen around the newest of the antirheumatic drugs, phenylbutazone (marketed under the trade name of Butazolidin®) owing principally to the fact that it causes serious toxic side effects in some patients, although in most instances these effects are minor and rapidly reversible.

Phenylbutazone is a pyrazole derivative related to aminopyrine. It was first used as a solvent for aminopyrine to permit parenteral administration of that drug. Soon it was observed that phenylbutazone has potent antirheumatic properties of its own, and it has been used by itself for the past 18 to 24 months. In laboratory studies the drug was observed to have analgesic, antihistaminic and antipyretic properties, and to decrease capillary permeability.[6, 16, 20] It is rapidly absorbed when given orally, and somewhat less so when given intramuscularly. The highest concentration in the plasma after a single dose occurs in two hours when it is given by mouth, and in six to ten hours when injected intramuscularly.[3] One third of the drug contained in the plasma is strongly bound to the plasma protein. With repeated daily dosage the amount in the plasma is remarkably constant in each patient, but the level of constancy varies considerably between patients. It ranges from 60 mg. per liter in some cases to 140 mg. in others. When that level is reached, increased dosage does not increase the amount in the plasma, the excess presumably being rapidly metabolized and excreted. It is thought that sodium retention occurs when the content of phenylbutazone in the plasma reaches 50 mg. per liter, but there is no anti-inflammatory effect until a level of 100 mg. per liter is reached. When the drug is discontinued, it takes approximately seven to ten days for total excretion of it.[2, 3, 16]

There is no doubt in the opinion of almost all observers who have written about phenylbutazone that it provides varying degrees of relief of pain in a majority of patients with rheumatic diseases, and to a lesser degree decreases swelling and increases mobility of the affected parts. The relief usually occurs within two or three days after administration is begun and the effect is completely dissipated within seven to ten days after it is discontinued. It is important to recognize that phenylbutazone, like the steroids, has no curative properties.

The most dramatic effect of the drug is in acute gout, where it promptly brings about pronounced relief in 80 to 85 per cent of cases—sometimes complete remission within 24 to 48 hours. It is reported to be of value in maintenance therapy of chronic gout, but since there are other less toxic drugs, such as colchicine and probenecid, which are relatively effective in such cases, it is not recommended for routine use.[11, 16, 19, 21] Phenylbutazone is also very effective in relief of pain in nonarticular rheumatism, such as "painful shoulder" and bursitis, but remissions may not be as complete or lasting as in gout.[25]

In rheumatoid arthritis, 50 to 80 per cent of patients get varying degrees of subjective relief of pain. The drug seems to be slightly more effective in the spondylitic than in the peripheral type of the disease. There is some disagreement as to objective relief obtained by use of phenylbutazone, but in a review of the literature it appeared that some objective improvement was noted in about 50 per cent of patients.

Phenylbutazone is also effective in the relief of symptoms in degenerative arthritis in a smaller proportion of patients, but its use in this disease is not ordinarily advised because of the age of the patients (for reasons stated below). It may be said that

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the effectiveness of phenylbutazone in the treatment of chronic rheumatic diseases is roughly inversely proportional to the duration of the disease.[12, 16, 22, 25, 27, 28, 32]

Toxic reactions occur in about 25 per cent of patients receiving phenylbutazone, but only in about 10 per cent is it necessary to discontinue administration. The common reactions are gastrointestinal upset, edema and rash. Less common is the occurrence of more generalized allergic reactions with stomatitis, purpura, hematuria and agranulocytosis. Several patients have died of agranulocytosis. Reactivation of preexisting peptic ulcer has occurred, and several cases of unexplained gastrointestinal bleeding have been reported.* Another reaction not reported, which the author has observed, is moderate to pronounced increase in blood pressure, with or without obvious edema. One investigator reported the occurrence of optic neuritis during the administration of phenylbutazone, but the status of the case is as yet not well defined.[7]

From the foregoing it is obvious that the value of phenylbutazone in the relief of symptoms of rheumatic diseases is now generally accepted, and that the drug sometimes causes undesirable and occasionally serious side effects. However, it is for use in dealing with a group of diseases which are notably difficult to control and, as yet, impossible to "cure," and for which there are relatively few effective drugs. Certainly, the incidence of toxic reactions to gold is almost as high as to phenylbutazone, and the dangers just about as great, although when gold is effective the improvement is prolonged. The use of steroids, corticotropin (ACTH) and cortisone, causes almost as many immediate side effects and no one knows what the really long term administration of them will produce. Physicians continue to use these drugs, but with great care. The author believes that the same should apply to the use of phenylbutazone; that both the good and the bad features of the drug should be recognized and constant vigil kept for the development of known and unknown side effects.

The following recommendations are offered:

Phenylbutazone is a valuable adjunct to the armamentarium available in the treatment of rheumatic diseases, but it is also a potentially dangerous drug and must be treated as such. Whether the drug should be used or not depends upon the real need for relief provided by it, balanced against the danger of possible toxic reactions. Certainly it should not be used in cases in which other less toxic drugs will provide as adequate, or nearly as adequate, relief.

Phenylbutazone should not be given to patients with a history of peptic ulcer and it should be used with great caution, if at all, in patients with a history of allergic reaction to drugs. In patients over 60 years of age and in others with known cardiac disease, or any disease complicated by edema, the intake of sodium should be restricted, if phenylbutazone is to be given at all.

Dosage of the drug should obviously be kept at a minimum;[9,13] never should it exceed 800 mg. daily.[12] It is now quite clear that larger dosage does not increase effectiveness. In some few cases, adequate relief can be obtained with doses of 100 mg. daily, or even less.

The drug should be taken with food, or with an anti-acid preparation that contains no sodium, to minimize gastric irritation. If the patient is given adequate amounts of phenylbutazone yet has no relief of symptoms within four to seven days, administration should be discontinued, for it is extremely unlikely that any improvement will occur. Patients should never be given prescriptions for large amounts of the drug, lest they neglect regular visits to the physician.[10]

The blood should be examined before administration of the drug is started, at frequent intervals during the institution of treatment, and regularly thereafter as long as therapy is continued. At each visit to the office, the physician should weigh the patient,[9] determine the blood pressure, and question him as to subjective symptoms. The author also believes that when phenylbutazone is given to a patient with a chronic rheumatic disease, he should be fully informed as to its lack of curative properties and its potential toxic effects, so that he can better cooperate with the physician.

In general, phenylbutazone should not be used by a physician who is not willing, or able, to accept the responsibility of careful continuous observation of each patient receiving the drug.

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